AMENDMENTS AND UPDATES TO HUMAN GENE TRANSFER PROTOCOLS

RECOMBINANT DNA ADVISORY COMMITTEE MEETING June, 2001

ID #	Letter	Protocol #	Amendment Description	
		9412-097	**Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study. Sponsor: Schering Plough Corporation (formerly Canji)**	
68	3/29/2001		*Protocol Change:*	Following changes have been made: Only two individuals, instead of three, will be enrolled at the highest dose. Individuals will not be followed beyond 28 days, unless adverse events are ongoing. Toxicity will not be evaluated beyond 28 days past the last cycle, unless adverse events are ongoing.
		9503-103	**Gene Therapy for AIDS using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins.**	
54	2/14/2001		*Annual Update:*	This amendment adds adverse event reporting and data safety and monitoring plans to the protocol. The investigators last submitted an annual report to our files in May, 2000. There have been no recent patients enrolled (last infusion was in 5/99). To date, 10 patients have received a total of 19 infusions. No further patients will be enrolled until a DSMB reviews the data from these patients (of note, this is being done NOT due to safety concerns but so as to comply with recent NIH guidance regarding periodic DSMB reviews of intramural protocols). OBA staff has reviewed the SAEs submitted and none are of major concern or unexpected in nature. The investigators have indicated that the DSMB has not, as of 03/29/01, reviewed the data. Further, once the DSMB has completed its review, the investigators will be certain to forward the DSMB recommendations.
136	3/29/2001		*Annual Update:*	Received copy of IRB approval of continuing review.

ID #	Letter	Protocol #	Amendment Description	
		9506-109	**Treatment of Patients with Advanced Epithelial Ovarian Cancer using Anti-CD3 Stimulated Peripheral Blood Lymphocytes Transduced with a Gene Encoding a Chimeric T-cell Receptor Reactive with Folate Binding Protein.**	
59	2/13/2001		*Protocol Change:*	Received documentation from the NIH Institutional Biosafety Committee that allows for changes so as to augment the longevity of the anti-CD3 stimulated peripheral blood lymphocytes transduced with a gene encoding a chimeric T-cell receptor reaction with folate binding protein. These changes were approved by the NIH IBC on 2-7-01. To date, 6 patients have been treated at the highest dose allowed in the original protocol. One patient had a SAE (pulmonary distress 2 hours after infusion, possibly related to the high-volume infusion) and this was reported to OBA last year.
		9511-134	**Phase I Study to Evaluate the Safety and In Vivo Persistence of Adoptively Transferred Autologous CD4+ T Cells Genetically Modified to Resist HIV Replication.**	
75	3/19/2001		*Protocol Change:*	Trial is closed to new accrual. Follow-up will continue.
		9512-138	**A Phase I Study of the Safety of Injecting Malignant Glioma Patients with Irradiated TGF-β2 Antisense Gene Modified Autologous Tumor Cells.**	
95	4/19/2001		*Other:*	Received copy of sterility test results for archived sample of material used for third individual. A positive result for staphylococcus was obtained on one out of two tests. Subsequent testing was negative for staphylococcus contamination.
143	5/ 2/2001		*Annual Update:*	To date six individuals have entered into this study, out of 9-12 planned for inclusion. Of the six, four completed the study and two dropped out and opted for conventional chemotherapy.
		9611-165	**Phase I Trial In Patients With Metastatic Melanoma Of Immunization With A Recombinant Fowlpox Virus Encoding the GP100 Melanoma Antigen.**	
137	4/ 3/2001		*Protocol Change:*	Due to transient grade 2 hypotension observed in several individuals in the second cohort, the clinical protocol and informed consent document have been modified to state that hypotension may occur in response to fowlpox administration.

ID #	Letter	Protocol #	Amendment Description
		9701-172	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study.**
53	2/14/2001		*Annual Update:* Received a supplement to protocol 9701-172. The supplement essentially consisted of a new 1571 Form (for the IND for this protocol, namely BB 6886) and a brief annual report. The study is closed to patient accrual but patients are still being followed up indefinitely due to the use of a retroviral vector. No replication competent retroviruses have been found in the annual samples submitted by the 8 surviving patients (of the 12 enrolled).
63	2/14/2001		*Annual Update:* The protocol is closed to accrual and 8 patients are still being followed on an annual and prn basis. All told, 12 patients were enrolled. Since last year's annual report, there have been no SAEs. The vector used was a retrovirus, and as such replication competent retroviruses are looked for. None were detected (using a S+/L- assay) and no viral envelopes were detected by PCR. The principal investigators recently published an article in Nature Medicine (June, 2000) describing the efficient retrovirus-mediated transfer of the MDR-1 gene into autologous human long-term repopulating hematopoietic stem cells. There is continued marking in some patients up to 2 years out. The article was enclosed with the annual report. The SAEs for this protocol were reviewed by OBA staff. There was one of concern from circa 18 months ago where a patient developed avascular necrosis of the femoral head approximately 9 months after receiving the gene transfer product. However, the investigators believed that this was due to the large amounts of chemotherapy that this patient received and supplied a literature search to support this. The animal studies also do not seem to support a tie-in between this product and the SAE. Otherwise, no new SAE reports found.
		9701-173	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine(PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O6-Methylguanine DNA Methyltransferase.**
85	2/20/2001		*Status Change:* Trial as of 2-20-01 has been closed to new research participant enrollment. Last individual was enrolled approximately one year ago. Follow-up will continue as outlined in the clinical protocol.

ID #	Letter	Protocol #	Amendment Description
		9703-181	**A Phase II Study of the Activity and Safety of Autologous CD4-Zeta Gene-Modified T Cells With or Without Exogenous Interleukin-2 in HIV Infected Patients. Sponsor: Cell Genesys, Inc.**
80	4/ 9/2001		*Status Change:* Notification from sponsor that trial is closed.
		9707-198	**A Phase I/II Study of Autologous CC49-Zeta Gene-Modified T Cells and alpha-Interferon in Patients with Advanced Colorectal Carcinomas Expressing the Tumor-Associated Antigen, TAG-72. Sponsor: Cell Genesys, Inc.**
81	4/ 9/2001		*Status Change:* Notification from sponsor that trial is closed.
		9709-210	**Compassionate Use Protocol for Retreatment with Allovectin-7 Immunotherapy for Metastatic Cancer by Direct Gene Transfer. Sponsor: Vical, Inc.**
77	3/28/2001		*PI or Site Change:* Dr. Frank Dunphy, Saint Louis University Health Sciences Center, is now a PI.
100	3/29/2001		*PI or Site Change:* Dr. Taral Patel, at the Columbus Community Clinical Oncology Program, is now a PI.
		9709-214	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis (formerly Gencell)**
55	3/ 2/2001		*Status Change:* Trial is officially terminated at the University of Pittsburgh site.
		9802-238	**Phase 1/2 Study of the Effects of Ascending Doses of Adenovirus Mediated Human FGF-4 Gene Transfer in Patients with Stable Exertional Angina. Sponsor: Berlex Laboratories, Inc.**
146	1/26/2001		*Annual Update:* An annual report for protocol 9802-238 was submitted to OBA on January 26, 2001.
		9802-239	**A Phase I/II Study of Hepatic Infusion of Autologous CC49-Zeta Gene-Modified T Cells in Patients with Hepatic Metastasis from Colorectal Cancer. Sponsor: Cell Genesys, Inc.**
82	4/ 9/2001		*Status Change:* Notification from sponsor that trial is closed.

ID #	Letter	Protocol #	Amendment Description
		9803-242	**A Phase I Study of CD 154 Gene-Transduced Leukemia Cells in Patients with Chronic Lymphocytic Leukemia.**
72	3/20/2001		*Status Change:* Notification from Immunogenex, Inc. (now the sponsor) that this trial is completed.
		9804-247	**A Phase I Safety Study of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A. Sponsor: Transkaryotic Therapies, Inc.**
47	2/26/2001		*Protocol Change:* With this amendment, the sponsor (Transkaryotic Therapies) is proposing to allow the investigator to perform a Factor VIII pharmacokinetic study in patients for whom this sort of data are not available. This information is of importance to the clinical management of these patients and also will help to identify the actual additive effect of the transfected autologous human fibroblasts that are to be producing Human Factor VIII. The amendment has been approved by the IRB at Beth Israel Deaconess Medical Center (Boston) and The informed consent document has been amended appropriately. The amount of blood that will be needed is 55 cc over a 48 hour time period. In addition, OBA staff has reviewed the latest SAE submissions for this protocol, and there are none that raise concern about possible immune responses to the autologous fibroblasts or to the produced HF VIII protein.
		9810-268	**Treatment of Patients with Stage IV Renal Cell Carcinoma with B7-1 Gene-Modified Autologous Tumor Cells and Systemic IL-2.**
130	3/29/2001		*Status Change:* Trial has met accrual goal and is now closed. *Annual Update:* Nineteen individuals were enrolled in this trial; five at dose level 1, five at level 2, and four at level 3. Three individuals did not produce enough vaccine cells to be administered the lowest dose. These individuals did, however, receive at their request fewer than the minimum number of cells (which was approved by the IRB).

ID #	Letter	Protocol #	Amendment Description	
		9901-280	**A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with >0.5 cm and <2 cm Residual Disease Following Surgery. Sponsor: Schering Corporation**	
62	2/21/2001		*Annual Update:*	To date, three patients have been entered at the University Medical Center of Southern Nevada (PI: Dr. Ellerton) site.
65	4/10/2001		*Status Change:*	Trial is closed at the following sites: 1) Johns Hopkins Scholl of Medicine (PI: Dr. Bristow). No individuals were enrolled at this site. 2) Mercy Hospital of Pittsburgh (PI: Dr. Christopherson) 3) University of Kentucky Medical Center (PI: Dr. Gallion). One individual enrolled. Follow-up will continue as outlined in the protocol. 4) Sharp HealthCare, Sidney Kimmel Cancer Center (PI: Dr. Gutheil) 5) University of Kansas School of Medicine (PI: Dr. Delmore)
67	5/ 1/2001		*Status Change:*	Trial is closed at the University of Medicine and Dentistry of New Jersey (PI: Dr. Rocereto)
		9901-281	**Phase I/II Trial of the Safety, Immunogenicity, and Efficacy of Autologous Dendritic Cells Transduced with Adenoviruses Encoding the MART-1 and gp100 Melanoma Antigens Administered With or Without Low Dose Recombinant Interleukin-2 (rIL-2) in Patients with Stage IV Melanoma. Sponsor: Genzyme Molecular Oncology**	
133	3/29/2001		*Protocol Change:*	The following changes have been made: 1) Only individuals with Stage III or IV primary cutaneous melanoma are eligible for this trial. Individuals with primary ocular or mucosal melanoma are not eligible. 2) Opthalmologic changes will be discussed with the FDA on a case-by-case basis. Individuals will not automatically be withdrawn from the study. 3) Third exclusion criteria for autoimmune disease has been amended to only automatically exclude individuals with clinically significant symptoms. Individuals with remote and/or clinically inactive systemic autoimmune diseases will not automatically be excluded. 4) Dose limiting toxicity is defined as any Grade 3 or 4 toxicity as outlined in the Common Toxicity Criteria that is considered to be (by the investigator and sponsor) to be possibly, probably, or definitely related to the study agent. This was previously defined in a memo to the clinical file and has now been incorporated into the protocol.

ID #	Letter	Protocol #	Amendment Description	
		9901-282	**A Phase II Randomized Trial of Recombinant Fowlpox and Recombinant Vaccinia Virus Expressing PSA in Patients with Adenocarcinoma of the Prostate. Sponsor: National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP).**	
135	4/27/2001		*Annual Update:*	Amendments were made to: (i) clarify entry criteria; (ii) proper disposal of material that comes into contact with study agent and proper care of injection site; and (iii) information has been added regarding Vaccinia Immune Globulin therapy.
		9901-283	**Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Cell Vaccines (Allogeneic Prostate GVAXTM) in Hormone-Naive Prostate Cancer Patients. Sponsor: Cell Genesys**	
83	4/ 9/2001		*Status Change:*	Notification from sponsor that trial is closed.
		9902-285	**A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.**	
56	3/ 2/2001		*Status Change:*	Trial is officially terminated.
52	3/ 9/2001		*Annual Update:*	Received submission to RAC protocol #9902-285 (UPCI #98-025) which contained the IRB approval letter (dated March 6, 2001), the recent modifications to the patient consent form and to the study protocol, and the annual IBC approval.

ID #	Letter	Protocol #	Amendment Description
		9902-287	**Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
71	3/20/2001		*Protocol Change:* Clinical protocol has been amended to indicate that individuals may re-start administration of adenovirus p53, if stopped for reasons other than toxicity. Tests that are required for individuals to re-start have been detailed.
		9902-292	**Immunization of Patients with Metastatic Melanoma Using a Recombinant Fowlpox Virus Encoding a GP 100 Peptide Preceded by an Endoplasmic Reticulum Insertion Signal Sequence. Sponsor: NCI-Cancer Therapy Evaluation Program (NCI-CTEP)**
60	2/13/2001		*Other:* Received a submission from the NIH IBC regarding protocol changes to protocol 292 (Dr. Rosenberg, principal investigator). The changes reflect revised NCI guidelines for Expedited Adverse Event Reporting and the requirements for a DSMB. As per the IBC approval (which occurred on 2-7-01) these changes do not significantly impact patient safety or protocol design or conduct and are deemed as administrative. The IBC approval letter was sent to this OBA on 2-13-01.
		9903-303	**Tumor Purging of Autologous Stem Cell Grafts in Children with High-Risk Solid Tumors: Transplantation of Retrovirally Marked Stem Cell Grafts Purified by CD34+ Antibody Selection and High-Speed Cell Sorting.**
132	3/28/2001		*Protocol Change:* This marking study will now use a Moloney-based retroviral vector expressing the human dihydrofolate reductase gene.

ID #	Letter	Protocol #	Amendment Description	
		9904-304	**Pediatric Phase I Study of AdV/RSV-TK Followed by Ganciclovir for Retinoblastoma**	
57	3/20/2001		*Annual Update:*	This amendment details changes made to the initial protocol. Essentially, the protocol approved by the FDA and reviewed by the RAC called for the treatment of retinoblastoma patients who had bilateral involvement. Additionally, one eye was to be already enucleated with the second having failed traditional chemotherapeutic and radiation therapies. This way, the initial study of Dr. Hurwitz's gene transfer product would be in patients with little hope of recovery (of note, the cure rate for retinoblastoma is in the low 90% if caught early. Only in patients where the disease is extensive at the time of diagnosis is the cure rate poor. With this in mind, the RAC recommended that the initial patients enrolled be those in the latter category due to their poor prognosis). Two patients were enrolled into the study, both meeting the above criteria. Both had injection of the gene transfer product (an adenovirus bearing the HSV TK gene) into the remaining affected eye. One patient appeared to have no response to the gene transfer product, but also had no adverse events seen. The other had a reduction in the size of the largest tumor plus an elimination of vitreal seeding by tumor cells. However, this patient also had a significant inflammatory response to the injected gene transfer product which responded adequately to topical steroids. Both patients needed to have their treated eyes enucleated due to progression of tumor (note, that only the largest tumor was injected. In both cases, multiple tumors were present). Due to the response seen in the second patient, Dr. Hurwitz amended the protocol to allow for the inclusion of patients with unilateral retinoblastoma. This was done so as to start evaluating the effect of the product in patients for whom this "therapy" is being developed (essentially in patients with unilateral disease where enucleation is trying to be avoided. This is only possible in situations where the tumor load is small enough so as to allow for local laser ablation or cryoablation. The gene product will be used, if all works out well, to reduce tumor load to a size small enough so as to allow this to happen.) It is noted in the revised protocol that the FDA and local IRB have approved this but no documentation is provided. An email was sent to Dr. Hurwitz to provide us with documentation of FDA, IRB and IBC approval of this amendment.
		9905-313	**Immunization of Patients with Metastatic Melanoma Using Recombinant Fowlpox and Vaccinia Viruses Encoding the Tyrosinase Antigen.**	
134	4/ 3/2001		*Annual Update:*	Received copy of the latest protocol and informed consent.

ID #	Letter	Protocol #	Amendment Description	
		9905-315	**A Phase I/II Study of a Prime-Boost Schedule of Human GM-CSF Gene Transduced Irradiated Prostate Allogeneic Cancer Vaccine (Allogeneic Prostate GVAX TM) in Hormone-Refractory Prostate Cancer (G9803) . Sponsor: Cell Genesys, Inc.**	
84	4/ 9/2001		*Status Change:*	Notification from sponsor that trial is closed.
		9905-318	**A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver. Sponsor: Schering Corporation.**	
69	3/29/2001		*Protocol Change:*	For those sites that did enroll individuals, adverse events that have not resolved by the end of the fifth cycle will continue to be evaluated/followed during the follow-up period. Survival will be monitored by telephone biannually for the research participant's lifetime.
			Status Change:	Notification from the sponsor (Schering-Plough) that this study is closed to new enrollment at all sites.
66	4/10/2001		*Status Change:*	Study is closed at the following sites: 1) University of Louisville (PI: Dr. McMasters). No individuals enrolled at this site. 2) University of Washington (PI: Dr. Gold). No individuals enrolled at this site. 3) Montefiore Medical Center (PI: Dr. Ravikumar) 4) University of California, Los Angeles (PI: Dr. Amado)

ID #	Letter	Protocol #	Amendment Description
		9907-327	**A Phase I Double-Blind, Placebo Controlled, Escalating Dose, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation**
64	3/ 7/2001		Please note that this amendment is applicable to protocols 9907-328 and 9907-329 too. The amendment documents several changes in the diagnostic studies that will be performed on the enrolled patients (for example, the use of 3-dimensional Magnetic Resonance Angiogram (MRA) compared to a 2-dimensional) and a change in the inclusion criteria. The changes appear reasonable and will most likely enhance the studies. OBA staff has also reviewed all of the SAEs reported for these 3 protocols and there are none that are of a nature that would require further information.
140	4/23/2001		*PI or Site Change:* Dr. John Laird, Washington Hospital Center, is now a PI.
		9907-328	**A Phase I, Open-Label, Multi-Center Extension Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation**
141	4/23/2001		*PI or Site Change:* Dr. John Laird, Washington Hospital Center, is now a PI

ID #	Letter	Protocol #	Amendment Description
		9907-329	**A Phase I, Open-Label, Single Dose, Roll-Over, Multi-Center Study of Ad2/Hypoxia Inducible Factor (HIF)-1?/VP16 Gene Transfer Administered by Intramuscular Injection to Patients with Critical Limb Ischemia Who are Not Candidates for Surgical or Percutaneous Revascularization. Sponsor: Genzyme Corporation**
142	4/23/2001		*PI or Site Change:* Dr. John Laird, Washington Hospital Center, is now a PI
		9908-337	**Transduction of CD34+ Cells from the Umbilical Cord Blood of Infants or the Bone Marrow of Children with Adenosine Deaminase (ADA)-Deficient Severe Combined Immunodeficiency (SCID)**
94	3/ 8/2001		*PI or Site Change:* *Other:* Received a request for a single individual exemption. This request was reviewed by OBA staff and the RAC Chair. A letter was sent to the investigators documenting the questions rasied during the review and the response.
		9910-346	**A Phase II, Randomized, Multicenter, 26-Week Study to Assess the Efficacy and Safety of CI-1023 Delivered Through Minimally Invasive Surgery Versus Maximum Medical Treatment in Patients with Severe Angina, Advanced Coronary Artery Disease, and No Options for Revascularization. Sponsor: Parke-Davis Pharmaceutical**
87	4/ 2/2001		*PI or Site Change:* Dr. Nabil Dib, at the Arizona Heart Institute & Foundation, is now a PI.

ID #	Letter	Protocol #	Amendment Description	
		9910-350	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer. Sponsor: Targeted Genetics Corporation**	
70	2/27/2001		*PI or Site Change:*	Dr. Paul Weiden at the Virginia Mason Medical Center is now a PI.
			Protocol Change:	Modifications to the clinical protocol include: 1) Dose of paclitaxel in the MTD group is increased from 100 to 135mg/m2. 2) Neutropenia, a known side effect of paclitaxel, lasting five or more days will no longer be considered a dose limiting toxicity. If neutropenia does last five or more days, the dose of paclitaxel will be adjusted. 3) Dosing schedule is reduced from three to two days per cycle by the administration of E1A-lipid and placlitaxel on day 1 followed by cisplatin on day 2. Change is being done so that dosing schedule is less burdensome on the participants.
127	4/20/2001		*PI or Site Change:*	
			Protocol Change:	Amendment made to clinical protocol for the 6 individuals who will be administered the MTD. This group will be divided into two groups of three. The second group of three will receive E1A-lipid complex and cisplatin on the same day. This group will not receive paclitaxel. Change is being made to determine the feasibility of administration, for future trials, of these two agents on the same day.

ID #	Letter	Protocol #	Amendment Description	
		9912-366	**A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety off Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division (formerly Rhone-Poulenc Rorer)**	
110	2/13/2001		*PI or Site Change:*	Dr. Patrick Cobb, at Billings Oncology Associates, is now a PI.
111	2/16/2001		*PI or Site Change:*	Dr. Stephen Williamson, at the University of Kansas, is now a PI.
112	2/20/2001		*PI or Site Change:*	The following PIs all located in Spain have been added: Dr. Alfredo Mena, Hospital General De Elche; Dr. Agusti Barnadas, Hospital Universitari Germans Trias I Pujol; Dr. J. Ma. Trigo, Hospital General Vall d'Hebron; Dr. Hernan Cortes-Funes, Hospital 12 de Octubre; Dr. Manuel Constenla, Complejo Hospitalario De Peontevedra; Dr. Emilio Fonseca Sanchez, Hospital Clinico de Salamanca; Dr. Andres Ruiperez, Hospital Clinico Universitaro; and Dr. Vicente Guillem, Instituto Valenciano de Oncologia.
113	2/22/2001		*PI or Site Change:*	Dr. Cherie-Ann Nathan, at Louisiana Stat University, is now a PI.
114	3/15/2001		*PI or Site Change:*	Dr. Sanjiv Agarwala, University of Pittsburgh, is now a PI.
115	5/ 1/2001		*PI or Site Change:*	Dr. Brian Buckey, Vanderbilt Clinic/Vanderbilt University Medical Center, is now a PI.
		9912-367	**Active Immunotherapy of Metastatic Renal Cell Carcinoma Using Autologous Dendritic Cells Transfected with Autologous Renal Tumor RNA.**	
79	3/19/2001		*Protocol Change:*	Specific stopping rules have been added for the generation of RNA transfected dendritic cells. These rules were added based upon NIH review for an RO1 grant application to fund this trial.
		0001-386	**Phase II Study of a B-7.1 Gene Modified Autologous Tumor Cell Vaccine and Systemic IL-2 for Patients with Stage IV Renal Cell Carcinoma.**	
131	3/29/2001		*Protocol Change:*	Vector for this study has been changed from an adenovirus to a canary pox virus. This is due to an inability to obtain the adenoviral vector from an outside institution. The canary pox virus contains the same transgene and will be supplied by CTEP/NCI. A copy of the revised clinical protocol and informed consent was provided.
		0001-387	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter, 12-Week Follow-up, Pilot Study of the Tolerability and Feasibility of Administering ADGVVEGF121.10 (CI-1023) Via the Biosense Intramyocardial Injection Device to Patients with Advanced Coronary Artery Disease. Sponsor: Parke-Davis Pharmaceutical Research**	
109	3/13/2001		*PI or Site Change:*	Dr. Barry Cohen, at the Morristown Memorial Hospital, is now a PI.

ID #	Letter	Protocol #	Amendment Description
		0002-388	**A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging, 26-Week Study to Assess the Safety and Efficacy of CI-1023 (ADGVVEGF121.10) in Peripheral Arterial Disease Patients with Severe, Disabling Intermittent Claudication. Sponsor: Parke-Davis Pharmaceutical Research**
108	12/19/2000		*PI or Site Change:* Dr. Brian Annex, at Duke University Medical Center, is now a PI.
121	1/24/2001		*PI or Site Change:* Dr. Corson, at the University of Iowa Hospitals and Clinics, is now a PI.
106	2/15/2001		*PI or Site Change:* Dr. Alan Hirsch, at the University of Minnesota, is now a PI.
125	4/20/2001		*PI or Site Change:* Dr. Raul Guzman, at Vanderbilt University Medical Center, is now a PI.
		0002-391	**Phase II Study of Leuvectin in Patients with Metastatic Renal Cell Carcinoma. Sponsor: Vical Inc.**
102	3/14/2001		*PI or Site Change:* Dr. Michael Morse, at Duke University Medical Center, is now a PI.
103	4/ 2/2001		*PI or Site Change:* Dr. John Amato, at Baylor College of Medicine, is now a PI.
		0004-393	**Phase II Study of a TGF-b2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in Patients with Non-Curable Non-Small Cell Lung Cancer. Sponsor: NovaRx**
88	4/24/2001		*Annual Update:* Received copy of annual report. To date, no individuals have been enrolled into this trial.
		0005-395	**A Phase I/II Trial Investigating the Safety and Immunotherapy of Adenovirus Encoding the Melan-A/MART-1 and gp100 Melanoma Antigens Administered Intradermally to Patients with Stage II-IV Melanoma. Sponsor: Genzyme Corporation**
58	2/28/2001		*Protocol Change:* On 2-28-01 the sponsor (Genzyme) submitted a facsimile regarding an amendment to OBA protocol 0005-395. This amendment was submitted to the FDA on the same date. The changes appear reasonable and seem to be an attempt to gather more information on possible immunologic responses to the sponsor's Melan-A/MART-1 and gp100 melanoma-specific antigens vaccine. In addition, additional information is provided regarding a serious adverse event in OBA protocol 9901-281, which is the sister protocol to this one. In that protocol a patient developed retinal changes which were noted after the 3rd vaccination. This SAE was discussed with the FDA (Drs. Keegan and Cardinali) on 10-20-00 and the patient was reentered into the study after agreeing to additional ophthalmologic examinations after each vaccine and re-consenting. This SAE was submitted to the OBA protocol 281 file in October of last year.

ID #	Letter	Protocol #	Amendment Description
		0005-399	**An Open-Label, Phase I, Dose-Escalation Study of Tumor Necrosis Factor-alpha (TNFeradeTM Biologic) Gene Therapy with Radiation Therapy for Locally Advanced, Recurrent, or Metastatic Solid Tumors. Sponsor: GenVec**
51	2/22/2001		*Other:* A revised protocol which incorporates suggestions from the RAC, FDA, IRB and IBCs at the two institutions, and from internal review at GenVec. These revisions have been reviewed by OBA and the changes made appear to be reasonable and add several safety procedures that will augment the study. One page summaries of pre-clinical mouse studies (of which there were two) demonstrating that the proposed human dose is well within the MTD for the mice.
		0006-402	**Phase I Study to Evaluate the Safety of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma Using Genetically-Modified Autologous CD8+ T Cell Clones.**
123	4/26/2001		*Protocol Change:* An amendment was made prior to final IBC and IRB approval and FDA authorization to revise the structure of the plasmid DNA. This change was made due to lack of sufficient expression to pass potency release criteria. The HyTk cDNA is now expressed from a separate promoter.
		0006-403	**A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Effect of Ad5FGF-4 on Myocardial Perfusion Defect Size and Safety in Patients with Stable Angina. Sponsor: Berlex Laboratories**
147	1/26/2001		*Annual Update:* Study 403 has not yet been initiated, with approximately 50 patients anticipated to be enrolled.
		0007-407	**A Phase I Double-blind, Placebo-Controlled, Escalating Dose, Multi-center Study of Ad2/Hypoxia Inducible Factor (HIF)-1-alpha/VP16 Gene Transfer Administration by Intramyocardial Injection During Coronary Artery Bypass Grafting (CABG) Surgery in Patients with Areas of Viable and Underperfused Myocardium not Amenable to Bypass Grafting or Percutaneous Intervention. Sponsor: Genzyme Corporation**
138	4/23/2001		*PI or Site Change:* Dr. Kevin Landolfo, at Duke University Medical Center, is now a PI.
139	4/23/2001		*PI or Site Change:* Dr. Mercedes Dullum, at Washington Hospital Center, is now a PI.
90	5/ 1/2001		*PI or Site Change:* Dr. Brian Cmolik, at University Hospitals of Cleveland, is now a PI.

ID #	Letter	Protocol #	Amendment Description
		0007-409	**A Phase I, Multi-Center, Open-Label, Dose-Escalation Study of the Safety and Tolerability of Intravenously Administered VLTS-587 in Patients with Solid Tumors and the Presence of Metastases or Primary Cancer in the Lungs. Sponsor: Valentis, Inc.**
122	2/23/2001		*Protocol Change:* The following has been added to the inclusion criteria: "...must have evaluable disease; must have failed one standard treatment or have no curative treatment option available; have at least 30 days elapsed between the last therapy for their tumor and the first treatment with VLTS-587 [study reagent] (Day 0);...; and a Karnofsky performance status of equal or greater than 80%." Following changes have been made to the exclusion criteria: "...must not have a C-reactive protein level greater than 1.0mg/dl; have a body temperature of greater than 101.5 F; have carbon monoxide diffusion capacity (DLCO), forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) levels of less than 65% of predicted value; have significant pleural effusion; have positive HIV status; have a history of heart failure (New York Heart Association Class III or greater); have a history of angina pectoris; have cardiac arrhythmias requiring treatment; have had an acute myocardial infarction (MI) within the last year prior to signing the informed consent..." Study participants will have at least 10 visits. One screening visit, two visits for administration of study reagent, one visit within 24 hours of administration of first dose, one visit 24 hours before administration of second dose, two follow-up visits at 7 and 14 days after second dose, and 3 monthly visits during long-term follow-up. Study participants will be admitted for a 24 hour observation period after the first dose.
78	3/27/2001		*PI or Site Change:* Dr. Scott Antonia, H. Lee Moffitt Cancer Center, is now a PI.
		0009-411	**Restenosis Gene Therapy Trial - Phase I Study (Regent I). Sponsor: Cardiogene Genetherapeutische Systeme AG**
119	4/19/2001		*PI or Site Change:* PI, Dr. Kuntz is now at the Brigham and Women's Hospital. *Protocol Change:* Additional information regarding biodistribution/toxicology has been added. Two new secondary endpoints have been added: 1) "MLD (in-stent and in-lesion) immediately after and 6 weeks after treatment with iNOS-lipoplex gene therapy and stent placement or ballone angioplasty" and 2) "Incidence of coronary perforation at conclusion of procedure as identified by the Angiographic Core Laboratory" An angiographic follow-up will now be required at 6 weeks in addition to 6 months. *Status Change:* This study has enrolled individuals in Germany. To date, no individuals have been enrolled at the US site.

ID #	Letter	Protocol #	Amendment Description	
		0009-412	**A Phase III, Multi-Center, Open-Label, Randomized Study to Compare the Effectiveness and Safety of Intratumoral Administration of RPR/INGN 201 in Combination with Chemotherapy Versus Chemotherapy Alone in 288 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Sponsor: Aventis Pharmaceuticals - Gencell Division**	
124	2/13/2001		*PI or Site Change:*	Dr. Patrick Cobb, at the Billings Oncology Associates, is now a PI.
48	3/ 6/2001		*PI or Site Change:*	Dr. John Hamm at Louisville Oncology in Louisville, KY is now a PI.
76	3/16/2001		*PI or Site Change:*	Dr. Jeffrey Spiro, University of Connecticut Health Center, is now a PI.
89	4/11/2001		*PI or Site Change:*	Dr. David Van Echo, at the University of Maryland, is now a PI.
105	5/ 4/2001		*PI or Site Change:*	Dr. George Yoo, at Wayne State University, is now a PI.
		0011-431	**A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma. Sponsor: Vical Inc.**	
101	3/ 2/2001		*PI or Site Change:*	Dr. Michael Atkins, at Beth Israel Deaconess Medical Center, is now a PI.
50	3/ 2/2001		*PI or Site Change:*	Dr. Eric Whitman, at Missouri Baptist Medical Center and The Melanoma Center of St. Louis, St. Louis, MO, is added as a PI.
97	4/10/2001		*PI or Site Change:*	Dr. Thomas Amatruda, at North Memorial Health Care/ Hubert H. Humphrey Cancer Center, is now a PI.
99	5/11/2001		*PI or Site Change:*	Dr. Michael Morse, Duke University, is now a PI.
		0011-432	**A Phase II Study of Safety and Efficacy of Allovectin-7 Immunotherapy for the Treatment of Primary Resectable Squamous Cell Carcinoma of the Oral Cavity or Oropharynx. Sponsor: Vical Inc.**	
104	3/ 2/2001		*PI or Site Change:*	Dr. Kerstin Stenson, at the Unigversity of Chicago, is now a PI.
86	4/16/2001		*PI or Site Change:*	Dr. Adriane Concus, at the Henry Ford Health System, is now a PI.
96	4/20/2001		*PI or Site Change:*	Dr. Gregory Wolf, at the University of Michigan Health System, is now a PI.